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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,843	12/02/2003	Hans Kurt Pingel	6207.520 -US	3225
23650	7590	08/09/2006	EXAMINER	
NOVO NORDISK, INC. PATENT DEPARTMENT 100 COLLEGE ROAD WEST PRINCETON, NJ 08540			SWOPE, SHERIDAN	
			ART UNIT	PAPER NUMBER
			1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/725,843

Applicant(s)

PINGEL ET AL.

Examiner

Sheridan L. Swope

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 17-24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/969,357.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1203</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-24 are pending.

Election/Restrictions

Applicants are thanked for pointing out that Claims 17 and 22 belong in Invention II, directed to a Factor VII polypeptide. The restriction requirement mailed December 1, 2005 is herein corrected as follows.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-16, drawn to a method for large-scale production of Factor VII, classified in class 435, subclass 69.1.
- II. Claims 18-19 and 22, drawn to a Factor VII polypeptide, classified in class 435, subclass 226.
- III. Claims 20 and 21, drawn to a composition comprising a plurality of Factor VII polypeptides, classified in class 435, subclass 226.
- IV. Claims 23 and 24, drawn to a method of treatment using a Factor VII polypeptide, classified in class 424, subclass 94.64.

The justification for said restriction requirement is as stated in the action of December 1, 2005.

First Action on the Merits

Applicant's election with traverse of Invention I, Claims 1-16, in their response of May 25, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-24 are pending. Claims 17-24 are withdrawn

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from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1-16 are hereby examined.

Priority

The priority date for the instant invention is taken to be October 2, 2001, the filing date of US 09/969,357, which disclose large scale production of a Factor VII polypeptide using medium lacking animal-derived components (pg 24).

Information Disclosure Statement-Objections

Parts of the Information Disclosure Statement filed December 2, 2003 (page 1) fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. Copies of initialed Information Disclosure Statements and Examiner provided 892 forms from other applications do not comply with 37CFR 1.98(a)1 (see MPEP 609.05(a)(b)). The information disclosure statement has been placed in the application file, but the information referred to on page 1 has not been considered. If Applicants wish for the references therein to be considered, a supplemental Information Disclosure Statement should be submitted. Any subsequent rejection, based on consideration of the supplemental Information Disclosure Statement, will not be considered a new grounds for rejection.

Title-Objections

The title is objected to for not being descriptive of the elected invention, which is a method.

Abstract-Objections

The abstract is objected to for not being descriptive of the elected invention, which is a method.

Specification-Objections

The specification, paragraph one, should be amended to up-date the recitation of the benefit of priority.

The specification is objected to for having a large, blank space on page 29.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The skilled artisan would not know the metes and bounds of the recited invention for the following reasons.

For Claim 7 the phrase “macrocarrier culture” renders the claim indefinite. The specification fails to provide a definition of said term and a search, of PubMed by the Office, failed to find any published reference with said phrase. Claim 8, as dependent from Claim 7, is rejected for the same reason.

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For Claim 10, the phrase “maintaining step comprises sedimentation” renders the claim indefinite. The skilled artisan would know that sedimentation would not support cell growth and is, therefore, not a “maintaining step”.

For Claim 14, the phrase “gradual or continuous” renders the claim indefinite because it is unclear whether Applicants meant to recite “gradual and continuous”, since it is unclear how, in a closed container, “gradual” is different from “continuous”.

For Claims 15 and 16, it is unclear whether the phrase “cells having a second predetermined density” means the cells are grown “to” a second predetermined density or the cells are stably maintained “at” a second predetermined density.

Claim 16 is rendered indefinite in reciting “large-scale production of Factor VII” as the method of Claim 16 fails to recite a process step for recovering Factor VII from the cell culture.

Additionally, Claims 2-14 are indefinite due to improper antecedent usage as follows.

For Claims 2-14, “A method as defined in claim...” should be corrected to “The method as defined in claim...”.

For Claims 2, 5, 6, and 12, “the cells” should be corrected to “the mammalian cells”.

For Claim 10, the phrase “the cell-containing carriers” lacks antecedent basis and, therefore, renders the claim indefinite. For purposes of examination, it is assumed that said phrase should be “the cells”.

For Claim 11, “the sedimentation” lacks antecedent basis. For purposes of examination, it is assumed that said phrase should be “sedimentation”.

For Claim 13, “wherein feeding” should be corrected to “wherein said feeding”.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for large-scale production of the Factor VII polypeptide used in Example 1, does not reasonably provide enablement for large-scale production of any Factor VII-related polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 1-16 are so broad as to encompass a method for large-scale production of any Factor VII- related polypeptide having any structure and any or no activity (specification, pg 6, parag 3). The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to a method for large-scale production of the extremely large number of polypeptides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID NO: 2 and the nucleotide sequence of SEQ ID NO: 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 1-16, which encompasses a method for large-scale production of all Factor-VII-related polypeptides, wherein the

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polypeptides have any structure and any or no activity. The specification does not support the broad scope of Claims 1-16 because the specification does not establish: (A) regions of any Factor VII polypeptide, from any species, that may be modified without effecting the desired activity; (B) the general tolerance of the desired activity to modification of any Factor VII polypeptide and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues of any Factor VII polypeptide with an expectation of obtaining a Factor VII-like polypeptide with the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for large-scale production of any number of Factor VII-like polypeptides with an enormous number of amino acid modifications of any Factor VII polypeptide from any species, wherein the Factor VII-like polypeptides have any or no activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession

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of the claimed invention. These claims are directed to a method for large-scale production of a genus of Factor VII-like polypeptides having any or no activity.

The specification does not contain any disclosure of the structure or function of all said Factor VII-like polypeptides. The genus of proteins that comprise these above polypeptide molecules is a large variable genus with the potentiality of having many different activities or not activity. Therefore, many functionally unrelated polypeptides are encompassed within the scope of these claims, including partial peptide sequences. The specification discloses the structure and function of only a single species of the claimed genus, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 5, 6, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Ragni et al, 2001 in view of Schmidtchen et al, 1998. Ragni et al review methods for large-scale, recombinant production of Factor VII. Ragni et al discuss the fact that recombinant

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Factor VII, used for treatment of haemophilia, is produced using serum and contains mouse IgG and BHK cell proteins (pg 31). Ragni et al further teach that even trace amounts of animal proteins are a potential means for transmission of viral infections (Abstract, lines 8-14). Ragni et al do not teach a method for producing recombinant Factor VII free of animal proteins. Schmidtchen et al teach a method for producing recombinant proteins in CHO cells using medium lacking animal-derived components. It would have been obvious to a person of ordinary skill in the art to use the method of Schmidtchen et al to prepare recombinant Factor VII in CHO cells using medium lacking animal-derived components. Suggestion and motivation to do so is provide by Ragni et al, wherein they state that there is a need to improve the margin of safety in treating bleeding disorders by producing recombinant clotting factors free of added proteins (Abstract, lines 1-6). The expectation of success is high, as recombinant production of Factor VII as well as recombinant production of proteins in medium lacking animal-derived components are both known in the art. Therefore, Claims 1, 2, 5, 6, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Ragni et al, 2001 in view of Schmidtchen et al, 1998.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ragni et al, 2001 in view of Schmidtchen et al, 1998 and further in view of Weikert et al, 1999 (IDS). The teachings of Ragni et al, 2001 and Schmidtchen et al, 1998 are described above. The combination of Ragni et al and Schmidtchen et al do not teach that the Factor VII produced thereby is differently glycosylated, compared to Factor VII produced in vivo or by BHK cells. Weikert et al teach a CHO cell line that has been engineered to over-express α 2,3-sialyl-transferase. It would have been obvious to a person of ordinary skill in the art to use the CHO

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cells of Weikert et al for large-scale production of Factor VII. Motivation to do so derives from the fact that, maximally sialylated proteins have a longer half-life in the blood stream (Weikert et al; pg 1116, parag 2 & pg 1119, parag 6). The expectation of success is high, as the CHO cells of Weikert et al are useful for expression of recombinant protein. Therefore, Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ragni et al, 2001 in view of Schmidtchen et al, 1998 and further in view of Weikert et al, 1999.

Claims 4 and 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Ragni et al, 2001 in view of Schmidtchen et al, 1998 and further in view of Chen et al, 1998. The teachings of Ragni et al, 2001 in view of Schmidtchen et al, 1998 are described above. The combination of Ragni et al and Schmidtchen et al do not specifically teach transferring a host cell culture to progressively larger size vessels (Claim 4), harvesting a portion of the culture and replacing with fresh medium (Claim 9), sedimentation of the cells (Claim 10), cooling prior to sedimentation (Claim 11), feeding with glucose (Claim 12), pulse feeding (Claim 13), or continuous feeding (Claim 14). However, said methods are standard in the art. For example, Chen et al teach transferring a host cell culture to progressively larger size vessels (basic protocol 6), harvesting a portion of the culture and replacing with fresh medium (alternate protocol 3), sedimentation of the cells (basic protocol 8), cooling prior to sedimentation (basic protocol 8), feeding with glucose (basic protocol 6), pulse feeding (basic protocol 7), or continuous feeding (alternate protocol 3). It would have been obvious to a person of ordinary skill in the art to use the teachings of Chen et al to adapt the method of Schmidtchen et al in order to prepare recombinant Factor VII. Reasons for making such adaptations are known in the art and are described by Chen et al (see above protocols). The expectation of success is high, as

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recombinant production of proteins using the adaptations of Chen et al are known in the art.

Therefore, Claims 4 and 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Ragni et al, 2001 in view of Schmidtchen et al, 1998 and further in view of Chen et al, 1998.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ragni et al, 2001 in view of Schmidtchen et al, 1998 and further in view of Reiter et al, 1990. The teachings of Ragni et al, 2001 and Schmidtchen et al, 1998 are described above. Neither Ragni et al nor Schmidtchen et al, or the combination thereof, teach the production of Factor VII using macroporous carriers. Reiter et al teach the use of a macroporous carrier for growth of CHO cells. It would have been obvious to a person of ordinary skill in the art to use the macroporous carrier of Reiter et al for large-scale production of Factor VII in CHO cells. Motivation to do so derives from the fact that, the concentration of CHO cells grown on said carriers reached a density 10-fold greater than growth on non-porous carriers. The expectation of success is high, as growing CHO cells on a macroporous carrier is known in the art. Therefore, Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ragni et al, 2001 in view of Schmidtchen et al, 1998 and further in view of Reiter et al, 1990.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
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A handwritten signature in black ink, appearing to be 'Swope', written over the printed name and title.